UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ASTRAZENECA AB, AKTIEBOLAGET HÄSSLE, ASTRAZENECA LP, KBI INC. and KBI-E INC., Plaintiffs and Counterclaim-Defendants, v. HANMI USA, INC., HANMI PHARMACEUTICAL CO., LTD., HANMI FINE CHEMICAL CO., LTD. and HANMI HOLDINGS CO., LTD., Defendants and Counterclaim-Plaintiffs.	Civil Action No. 3:11-CV-00760-JAP-TJB Judge Joel A. Pisano Magistrate Judge Tonianne J. Bongiovanni

SUPPLEMENTAL DECLARATION OF DR. STEPHEN G. DAVIES ON CLAIM CONSTRUCTION

I, STEPHEN G. DAVIES, a Citizen of Great Britain, DECLARE AS FOLLOWS:

I. EDUCATIONAL BACKGROUND AND QUALIFICATIONS

1. I make this declaration in further support of my Declaration of November 7, 2011, which was prepared in conjunction with AstraZeneca's initial Markman submission in this case. I incorporate my previous Declaration in its entirety.

2. In addition to the materials I have relied upon previously, I have considered the January 6, 2012 Supplemental Declaration of Dr. Jerry L. Atwood and attached exhibits, which was submitted in conjunction with Hanmi's Responsive Markman Brief. In addition to Dr. Atwood's Supplemental Declaration, I have also considered the transcript of Dr. Atwood's deposition and related exhibits, as well as the additional materials referred to in this declaration.

1. "Alkaline salt"

3. In his January 6, 2012 Supplemental Declaration, Dr. Atwood takes the position that my opinions of the ordinary meaning of "alkaline salt" are inconsistent with AstraZeneca's claim construction of that term. AstraZeneca proposed "alkaline salt" to mean a basic salt (here, a salt in which (–)-omeprazole is negatively charged) that is suitable for use in a pharmaceutical formulation.

4. A "salt" is made up of positively charged ions (cations) and negatively charged ions (anions) held together in the solid state by ionic bonds. In water, the individual ions that make up a salt tend to dissociate.

5. The ordinary meaning of "alkaline salt" of (–)-omeprazole to a person of ordinary skill in the art is not limited to a particular set of positively-charged cations. Dr. Atwood disagrees with my opinions on the ordinary meaning of "alkaline salt", because this meaning would encompass toxic salts.

6. Dr. Atwood, however, has failed to appreciate that AstraZeneca's proposed construction accounts for the fact that in the claims of the '504 patent, the "alkaline salt" is within a "pharmaceutical formulation for oral administration." In the context of claims to "pharmaceutical formulations for oral administration," a person of ordinary skill in the art would understand that the alkaline salts of the claims of the '504 patent are limited to those salts suitable for pharmaceutical use.

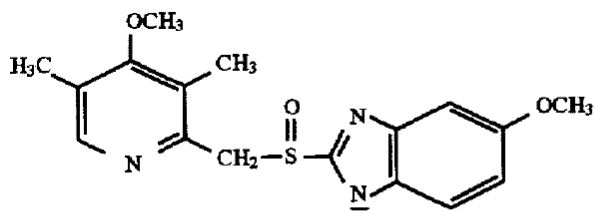
7. When the term "alkaline salt" is viewed within the context of the claims of the '504 patent, the meaning of the term is consistent with AstraZeneca's proposed construction.

8. As I opined in my Declaration of November 7, 2011, the term "alkaline salt" would ordinarily be understood to mean a salt that is basic—that is, one that generates basic solutions in water or that is generated under basic conditions. A person of ordinary skill in the art would understand that suitable cations for "alkaline salts" include, at least, cations of all of the metals in Groups I and II (lithium, sodium, potassium, rubidium, caesium, beryllium, magnesium, calcium, strontium or barium) as well as ammonium, but are not limited to these cations.

9. Scientific dictionaries support an ordinary meaning of "alkaline salt" that is not limited to specific cations.[1]

[1] See, e.g., Chambers Dictionary of Science and Technology, Revised Edition (1974): defining "alkali metals" to mean "lithium, sodium, potassium, rubidium, and caesium, all monovalent metals in the first group of the periodic system;" "alkaline earth metals" to mean "beryllium, magnesium, calcium, strontium, barium, and radium, all divalent metals in the second group of the periodic system;" "alkaline solution" to mean: "an aqueous solution containing more hydroxyl ions than hydrogen ions;" and "alkalinity" to mean: "The extent to which a solution is alkaline[, s]ee pH value." (D.I. 133.5, Exhibit 2; AZ0005145462–64). In chemistry, the degree of acidity or alkalinity of a solution is reflected by a numerical 'pH' scale. A pH of 7.0 is neutral. Solutions with a pH below 7.0 are acidic and solutions with a pH above 7.0 are basic (or alkaline).

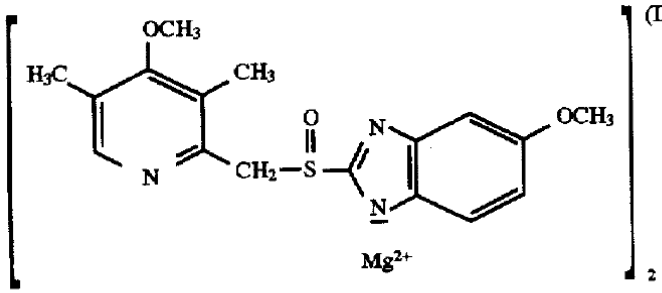
10. The patent specification and file history are also consistent with the ordinary meaning of "alkaline salt" discussed above. For example, the "most preferred" salts of the '504 patent are structures **I** and **II** in column 3, which depict individual enantiomers of omeprazole with a negative charge (deprotonated):[2]



(Ia, Ib)

Nat

Ia (+)-enantiomer
Ib (–)-enantiomer



(IIa, IIb)

IIa (+)-enantiomer
IIb (–)-enantiomer

As discussed above, these salts, in which an individual enantiomer of omeprazole is deprotonated, are basic, or alkaline.

11. In addition, the preparation of the "alkaline salts" of the '504 patent is described generally as involving treatment of a neutral enantiomer of omeprazole "with a base." Col. 4, ll. 51–61, l. 65 – col. 5, l. 4. Such preparation thus occurs under basic conditions, and results in an enantiomer of omeprazole that is deprotonated and anionic (and is not protonated and cationic as in an acid addition salt), just as in structures **I** and **II**.

[2] While the stereocentre in these compounds is not depicted in the same manner as above for the enantiomers of omeprazole, a person of ordinary skill still understands that the sulfur atom bears four distinct groups in each of the enantiomers of structures **I** and **II**.

12. Examples 1–3, 6 and 7 detail specific applications of this general procedure. In these examples, the "alkaline salts" of (–)-omeprazole are formed by deprotonation of neutral (–)-omeprazole with base (sodium hydroxide or magnesium methoxide) affording salts in which (–)-omeprazole bears a negative charge (is deprotonated).

13. In addition, all exemplary counterions for the salts of individual enantiomers of omeprazole that are mentioned throughout the specification are cationic (positively charged), which means the individual enantiomers of omeprazole must be anionic (negatively charged).

14. From a review of the specification and the prosecution history of the '504 patent, a person of ordinary skill in the art would understand that the term "alkaline salt" (of (–)-omeprazole) identifies (–)-omeprazole as the anion portion of the salt and does not limit the counterion to any particular cation.

15. The ordinary meaning of "alkaline salt" is entirely consistent with the specification and prosecution history of the '504 patent. In addition, Dr. Atwood also understands that the ordinary meaning of "alkaline salt" means a basic salt (here, a salt in which (–)-omeprazole is negatively charged). (D.I. 177.2; Atwood Tr. 72:6-76:14).

16. However, in the context of the claims to pharmaceutical compositions or methods of their use, a person of ordinary skill in the art would understand the term "alkaline salt" is limited to those alkaline salts that are suitable for pharmaceutical use. The claimed alkaline salts of (–)-omeprazole are limited to those salts that have properties that would not render the formulation unsuitable for pharmaceutical use.

17. Dr. Atwood suggests that the claims of the '504 patent encompass "hundreds of thousands" of possible cations. (D.I. 174.1; Supplemental Atwood Declaration ¶12). This is incorrect. In the context of the claimed "pharmaceutical formulations for oral administration," a

person of ordinary skill in the art would understand that the claims only include those basic or alkaline salts that are acceptable in a "pharmaceutical formulation for oral administration".

18. Dr. Atwood also shares this understanding, and acknowledges that the "alkaline salts" of the '504 patent claims cannot include all cations of (–)-omeprazole and excludes, for example, beryllium, cesium, rubidium, francium, radon and barium as "alkaline salts", because they are either radioactive or toxic. (D.I. 174.1; ¶¶13-23).

19. Dr. Atwood acknowledges that a person of ordinary skill in the art would recognize and understand that these metals are toxic at a level required to achieve a pharmaceutical effect of (–)-omeprazole. (D.I. 174.1; ¶23).

> Persons of ordinary skill in the art would understand that most metals referred to by Dr. Davies are toxic at a level required to achieve a pharmaceutical effect of (–)-omeprazole. For example, administration of a lead salt to humans would have disastrous consequences. [(D.I. 174.1; ¶23)]

20. Despite any toxicity, such salts would be understood by a person of ordinary skill in the art as "alkaline salts", but a person of ordinary skill in the art would also recognize that such salts are not suitable for pharmaceutical use, would not be included in a "pharmaceutical formulation" and would not fall within the scope of the "alkaline salts" of the claims of the '504 patent.

21. My opinions on the meaning of "alkaline salt" have not changed. I presented my opinion about the ordinary meaning of "alkaline salt" and that the claimed alkaline salts were limited to those salts that were suitable for pharmaceutical use in my Declaration of November 7, 2011, which was prepared in conjunction with AstraZeneca's initial Markman submission in this case (see at least ¶¶ 41, 42, 51 and 57).

22. During my deposition on my claim construction opinions, I also testified that an "alkaline salt", in the context of the claims of the '504 patent, is limited to a pharmaceutically

acceptable alkaline salt. (D.I. 177.1; Davies Tr. 64:3-8; 172:18-22 and 173:21-24). During the deposition, Hanmi's counsel acknowledged this position and opinion: "Would a person of ordinary skill in the art understand that the titanium salt of the (–)-enantiomer of omeprazole would have properties sufficient to make it pharmaceutically acceptable, as you've explained is part of the '504 patent claims?" (D.I. 177.1; 172:23 to 173:2).

23. The number of pharmaceutically acceptable species of alkaline salts of the claims of the '504 patent certainly exceeds the sodium, magnesium, lithium, potassium, calcium and quaternary ammonium (Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$) salts to which Hanmi limits it proposed construction.

24. This is clear from a review of the '504 patent, which identifies alkaline salts in addition to sodium, magnesium, lithium, potassium, calcium and quaternary ammonium. Specifically, the '504 patent notes (Col. 1, ll. 17–21) that "alkaline salts" of omeprazole in EP 124,495 ("EP '495") and its U.S. counterpart, U.S. Patent No. 4,738,974, include titanium and guanidinium as a species of "alkaline salts" (D.I. 133.5, Exh. 6; EP '495 (AZ0005144655–71) p. 2, ll. 19–35; p. 5, ll. 26–27, Examples 1–10; D.I. 133.5, Exh. 7; '974 patent (AZ0001414538–43) Col. 1, l. 67 to Col. 2, l. 23 and Col. 3, l. 49 and Examples 1–10). These "alkaline salts" (titanium and guanidinium) are not accounted for or listed by Dr. Atwood or by Hanmi in their proposed construction.

25. An examination of the '504 patent claims suggests that the claims encompass alkaline salts that include species in addition to sodium, magnesium, lithium, potassium, calcium or ammonium. Comparing claim 1 to dependent claim 3, and claims 6 and 7 to dependent claim 10, shows that the dependent claims specify the same options for "alkaline salts" that Hanmi has identified ("Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$ salt"), while the independent claims refer simply

to "alkaline salt." A person of ordinary skill would understand from the claims themselves that the "alkaline salts" in claims 1, 6 and 7 must include more cations than just "Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$" of dependent claims 3 and 10, as Hanmi suggests.

26. In addition, a person of ordinary skill would understand from the specification that the salt forms identified by Hanmi are merely examples:

> Alkaline salts of the single enantiomers of the invention are, as mentioned above, beside the sodium salts (compounds Ia and Ib) and the magnesium salts (compounds IIa and IIb), exemplified by their salts with Li^+, K^+, Ca^{2+} and $N^+(R)_4$[.]

Col. 5, ll. 7–11. The express language "exemplified by" conveys that the identified salt forms ("Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$") are merely examples of some (not all) of the possible "alkaline salts."

27. During prosecution, in a January 21, 1997 Examiner Interview Summary, the Examiner addressed the patentability of a proposed claim:

> A pharmaceutical formulation for oral administration of pure solid state (–) enantiomer of omeprazole Na-salt may be allowable after reviewing the data in affidavit form. . . . The scope of the claim will depend on the data submitted.

In a February 18, 1997 response and amendment, the Applicants discussed and submitted a declaration disclosing:

> clinical studies which involved both the monovalent sodium salt and the divalent magnesium salt of the (–)-enantiomer of omeprazole, ***thus supporting the full scope of the genus of alkaline salts disclosed in the application and as claimed herein, as suggested by the Examiner at the interview***. (Emphasis added)

The pending claims at the time were those that ultimately issued, and thus a person of ordinary skill would understand that the Examiner found the data on the sodium and magnesium salts sufficient to support the claims to "Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$ salt[s]" as well as the broader genus of "alkaline salts."

28. Hanmi's proposed construction also omits the Group II metal, strontium (an alkaline earth metal). A person of ordinary skill in the art would also understand that strontium falls within the literal meaning of "alkaline salt" of at least claim 1 of the '504 patent, because strontium salts have previously been used clinically in pharmaceutical formulations. (*See, e.g.*, the background discussions of prior clinical application of strontium salts as well as the list of references in Marie (1993) *J. Bone Min. Res.* 8(5): 607 (D.I. 133.5, Exh. 3; AZ0005145385–94); Marie (1986) *Metabolism* 35: 547 (D.I. 133.5, Exh. 4; AZ0005144147–51); and Marie (1985) *Miner. Electrolyte Metab.* 11: 5 (D.I. 133.5, Exh. 5; AZ0005145453–61). Hanmi's NDA product is a salt of anionic (deprotonated, thus basic)(–)-omeprazole with Sr^{2+} (strontium) as the cation.

29. Hanmi's proposed construction also omits several of the 21 cations identified in the Berge reference, cited by Dr. Atwood, as known to be fit for administration to humans.

30. Dr. Atwood also newly claims that a person of ordinary skill in the art could not prepare any basic salt, based on the methods of the '504 patent. (D.I. 174.1; ¶ 30). Dr. Atwood refers to statements made during my deposition and previous declarations in support for his positions. (D.I. 174.1; ¶¶ 30 and 31).

31. I have previously opined and testified that a person of ordinary skill in the art, at the priority date of the '504 patent would not have any expectation that a solid salt state salt of a single enantiomer of omeprazole could be formed. I note that Dr. Atwood agrees with this assessment. (D.I. 174.1; ¶ 32). At the priority date, no salts of a single enantiomer of omeprazole were known. Moreover, the properties of salts of single enantiomers of omeprazole, including salt formation, cannot be predicted from the salts of racemic omeprazole.

32. After the priority date of the '504 patent and publication of the corresponding PCT application (PCT/SE94/00509), a person of ordinary skill in the art would know from those

disclosures that the magnesium and sodium salts of the single enantiomers of omeprazole could be prepared and that the sodium salt could be prepared in a crystalline form, by following the methods of the '504 patent.

33. With the guidance and information provided by these applications and the '504 patent, a person of ordinary skill in the art could prepare the "alkaline salts" of the pharmaceutical formulations of the '504 patent claims without undue experimentation. Dr. Atwood has cited no evidence to the contrary.

34. As I explained in my Declaration of November 7, 2011 (¶¶ 19-25) enantiomers can be designated either by convention as (*R*) or (*S*), or by experimental measurement of their optical rotations as (+) or (–). For any specific enantiomer there is no correlation between these designators i.e. (*S*)-enantiomer of any chemical substance could be (+) or (–).

35. Esomeprazole is (*S*)-(–)-omeprazole which has the designators (*S*)-(–)- because by convention the configuration of the stereogenic centre is named (*S*)- and by experiment the optical rotations is (–)-.

36. Example 1 of the '504 patent describes the conversion of (*S*)-(–)-omeprazole to its sodium salt, a new chemical substance. A person of ordinary skill would know that this new chemical substance would still have the (*S*)-configuration by convention since nothing has happened chemically to perturb the configuration, but would not know the sign of the optical rotation: there is no correlation between the optical rotation of one chemical substance and another chemical substance.

37. A person of ordinary skill would understand from Example 1 of the '504 patent that (*S*)-omeprazole sodium salt has a measured (+)- optical rotation i.e. its designators are (*S*)-(+)-.

38. Similarly, from example 5 of the '504 patent, a person of ordinary in skill in the art would understand that (*S*)-omeprazole magnesium salt has a measured (–)- rotation i.e. its designators are (*S*)-(–)-.

39. There is no chemical basis for Dr. Attwood's new assertions in his Supplemental Declaration (D.I. 174.1; ¶¶ 27 and 28) that the configuration (*S*)- changes on formation of any salt. Indeed a person of ordinary skill would know this is impossible since were this to be the case (S)-omeprazole would racemise to a 50:50 mixture of enantiomers on treatment with base and the thus formed salts would therefore have zero optical rotation.

40. The disconnect between the designators (*R*)/(*S*) and (+)/(–) is common general knowledge. For example the commercially available (*S*)-lactic acid and its salts have the following properties

Chemical Substance	**Sign of rotation**
(*S*)-lactic acid	(+)
(*S*)-lactic acid sodium salt	(-)
(*S*)-lactic acid and magnesium salt	(-)
(*S*)-lactic acid silver salt	(+)

All the above have the same, (*S*), configuration but the sign of the optical rotation is random.

41. The methods of preparing the sodium and magnesium salts of the '504 patent are applicable to other basic salts. The change in sign of rotation has no bearing on the applicability of the methods to other salts and certainly does not demonstrate that other members of the genus of alkaline salts could not be performed according to the methods of the '504 patent, as Dr. Atwood claims. (D.I. 174.1; ¶ 28).

42. In view of the ordinary meaning of "alkaline salt", "pharmaceutical formulation", the claims, specification and prosecution history of the '504 patent, a person of ordinary skill in the art would understand "alkaline salt" to mean any basic salt (here, a salt in which (–)-

omeprazole is negatively charged) that is suitable for use in a pharmaceutical formulation, and to not be limited to the exemplary salt forms in the specification.

2. "pharmaceutically acceptable salt"

43. The term "pharmaceutically acceptable salt" appears expressly or by dependence in all of the asserted claims of the '192 patent.

44. The '192 patent states in column 1, before the "Field of the Invention" section:

> The description of salt forms of the single enantiomers of omeprazole and the process of making the same is herein incorporated by reference to copending Ser. No. 08/376,512.

Col. 1, ll. 10–13. U.S. Patent Application No. 08/376,512 is the application that issued as the '504 patent. In my opinion, based on this unambiguous statement, a person of ordinary skill would understand that the "pharmaceutically acceptable salts" of the '192 patent are the same as the "alkaline salts" of the '504 patent. Therefore, for all of the reasons stated above in the context of addressing the meaning of "alkaline salt" in the '504 patent claims, the "pharmaceutically acceptable salts" of the '192 patent claims would be understood to be basic salts, that is, ones in which (–)-omeprazole is negatively charged, and would not be limited to the exemplified salts Hanmi has proposed.

45. Hanmi interprets the term "pharmaceutically acceptable salt" to mean only those salt forms specifically named in the '504 patent ("Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$ salt"), or alternatively that the term embraces both "alkaline salts" and "acid addition salts." I disagree with both of these constructions.

46. I understand that Hanmi has pointed to column 4 of the '192 patent where it states that "the term 'pharmaceutically acceptable salt' refers to both acid and alkaline pharmaceutically acceptable non-toxic salts," which Hanmi cites presumably to support its alternate construction that the salts of the invention include acid addition salts. Col. 4, ll. 14–16.

A person of ordinary skill would not read this general definition of "pharmaceutically acceptable salt" as contradicting the statement in column 1 that the "description of salt forms of the single enantiomers of omeprazole" is as detailed in the '504 patent—i.e., alkaline salts.

47. First, this general definition for "pharmaceutically acceptable salt" appears in the context of a paragraph that is not limited to (–)-omeprazole as the only active pharmaceutical ingredient. Col. 4, ll. 9–19. In fact, this paragraph indicates that "other therapeutic ingredients are especially of interest in the treatment of Helicobacter infections." Col. 4, ll. 16–19.

> The pharmaceutical compositions of the present invention comprise the (–)-enantiomer of omeprazole as active ingredient, or a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salt" refers to both acid an alkaline pharmaceutically acceptable non-toxic salts. Compositions comprising other therapeutic ingredients are especially of interest in the treatment of Helicobacter infections. [Col. 4, ll. 9-19.]

48. The term "pharmaceutically acceptable salt" is not limited to the (–)-enantiomer of omeprazole, but applies to any therapeutic agents, specifically those agents combined with (–)-omeprazole in the treatment of Helicobacter infections. The "other therapeutic agents" need not be limited to alkaline salts, and may be employed as acid addition salts, thus explaining the reference to acid addition salts in the definition of "pharmaceutically acceptable salts." Critically, and as I discuss below, because (–)-omeprazole is highly unstable in acid, a skilled person would not consider an acid addition salt of (–)-omeprazole a pharmaceutically acceptable salt.

49. The acid instability of (–)-omeprazole is disclosed in the '504 patent. The '504 patent specification emphasizes "the surprising high stability in alkaline conditions for the compounds of the invention," in contrast to the "acidic conditions" employed in prior art in unsuccessful efforts to prepare "optically pure [individual enantiomers of] omeprazole." Compare col. 13, l. 31 – col. 14, l. 4 to col. 1, ll. 27–42 (noting that acidic conditions "would be

devastating" for the individual enantiomers of the invention). This known instability is also reflected in the declaration of Dr. Andersson submitted during prosecution of the '504 patent characterizing the enantiomers of omeprazole as "acid labile" (D.I. 133.2, Exh. 4 at AZ0005000175), as well as AstraZeneca's '974 and EP '495 patents that state that omeprazole is "susceptible to degradation in acid" (D.I. 133.5, Exh. 7 at col. 4, ll. 25–30 and Exh. 6 at 6).

50. Dr. Atwood refers to three patents and a publication to suggest that acid addition salts of omeprazole or (–)-omeprazole were known in the art. (D.I. 174.1; ¶¶ 53-56, citing D.I. 179.4-7). These references do not support Dr. Atwood's suggestion.

51. U.S. Patent No. 4,337,257 does not disclose acid addition salts of omeprazole. Instead, this patent discloses a large genus of millions of species and does not specifically identify or exemplify omeprazole or any specific salt of omeprazole or one of its enantiomers. (D.I. 174.1; ¶ 53; D.I. 179.4). This generalized disclosure does not provide a person of ordinary skill in the art with any motivation to prepare acid addition salts of omeprazole or demonstrate, as Dr. Atwood suggests, that acid addition salts of omeprazole or (–)-omeprazole were known.

52. U.S. Patent No. 5,066,652 is similarly general and does not specifically identify or exemplify omeprazole or any specific salt of omeprazole or one of its enantiomers nor does the disclosure relate to omeprazole. (D.I. 174.1; ¶ 54; D.I. 179.5). This patent does not "establish the existence of acid addition salts of omeprazole" as claimed by Dr. Atwood.

53. U.S. Patent No. 6,255,502 was not available at the priority date of the '192 patent. (D.I. 174.1; ¶ 55; D.I. 179.6). This patent includes omeprazole in a list of over one hundred compounds for which acid addition salts could be prepared. Again, however, no specific salts of omeprazole are disclosed or exemplified.

54. The Karthikeyan reference also was not available at the priority date of the '192 patent. (D.I. 174.1; ¶ 56; D.I. 179.7). Karthikeyan references the hydrochloride salt of racemic omeprazole but does not disclose the chemical stability or purity. Nothing in Karthikeyan suggests that this salt is sufficiently pure or stable to be pharmaceutically suitable.

55. The '504 patent refers to DE 4035455 (DE '455 application; D.I. 111.2) and methods of separating enantiomers of omeprazole. DE '455 uses highly acidic conditions that require neutralization to produce the neutral non-salt forms of enantiomers of substituted benzimidazoles. ('504 Patent; Col. 1; ll. 27-42). Dr. Atwood also refers to DE '455 to support his position that acid addition salts of individual enantiomers of omeprazole were known. (D.I. 174.1; ¶¶ 49-51).

56. I am very familiar with the DE '455 application. I have reviewed and commented on the DE '455 application and declarations and deposition transcripts of Bernhard Kohl and Jörg Senn-Bilfinger, inventors of the DE '455 methods.

57. The methods of DE '455 were originally developed with pantoprazole, a compound that, like omeprazole, acts as a proton pump inhibitor. (Exh. A; Declaration of J. Senn-Bilfinger ¶ 11). When the methods were applied to omeprazole, extensive degradation occurred and the product was an optically and chemically impure material (Example 6 of DE '455) that Drs. Kohl and Senn-Bilfinger considered unsuitable for pharmaceutical use. (Exh. A; Declaration of Jörg Senn-Bilfinger ¶¶ 11, 24, 25, 26 and 36-39; Exh. B; Declaration of Bernhard Kohl ¶¶ 43, 44, 91-93 and 101-107; Exh. C; Kohl Tr. 5:25 – 103:5; Exh. D; Senn-Bilfinger Tr. 6:7 – 41:10).

58. The laboratory notebooks and the declaration of Dr. Kohl show that the acid conditions of the methods of the DE '455 application had a devastating effect on omeprazole.

Dr. Kohl and his coworkers recorded total yields of between 1 and 4% for (+)-omeprazole in, at best, 90-92% e.e. (Exh. B; ¶¶ 68, 96 and 99; Exh. C; 64:12 – 95:18).

59. Extensive chemical degradation and loss of material was also observed by Magnus Larsson, an AstraZeneca scientist who evaluated the methods of DE '455 for use with omeprazole. (Exh. E; Declaration of Magnus Larsson ¶¶ 28). After multiple attempts, he was unable to obtain any material and the effort was abandoned. (Exh. E; ¶¶ 22, 30, 32, 33, and 36).

60. Dr. Atwood suggests that the (+)-omeprazole obtained in Example 6 was optically pure, based on an evaluation of optical rotation. The optical purity cannot be accurately determined or even reliably estimated in a sample that is known to be impure. Impurities such as degradation products, solvents and other contaminants can significantly influence the measured optical rotation. Based on the declarations of the inventors of the DE '455 application and the accompanying laboratory notebooks recording all the work that led to the DE '455 application, we know that the material obtained in Example 6 was chemically impure.

61. Although Dr. Atwood concludes that the material of Example 6 is optically pure, Dr. Kohl has submitted declarations in the European Patent Office and Canada, supported by analytical data, that he and his colleagues could achieve an enantiomeric purity of no better than 90-92% enantiomeric excess (Exh. B; ¶ 68; Exh. F; ¶ 68).

62. In view of the specifications, the file histories of the '192 and '504 patents, a person of ordinary skill would understand "pharmaceutically acceptable salt" to mean any basic salt (here, a salt in which (–)-omeprazole is negatively charged) that is suitable for pharmaceutical administration, and to not be limited to the exemplary salt forms in the '504 patent specification or to include acid addition salts.

63. I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Date: March 19, 2012

STEPHEN G. DAVIES